DETAILED ACTION

Applicants response filed 02/12/2010 is acknowledged.

Claim status:

Claims 1-3, 161-163, and 169 are under prosecution, while 4-160 and 164-168 are withdrawn.

Response to Remarks:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Previously presented rejection of claims 1-3, 161-163, and 169 under 35 U.S.C. 103(a) as obvious is maintained for reasons of record.

Rejection over Yamamoto et al. Chemical & Pharmaceutical Bulletin (1997), 45(8), 1282-1286.

Applicant's arguments were fully considered but are not persuasive.

Applicant's argue that:

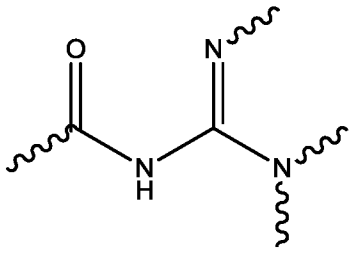
The variables Rj and Rk cannot be hydrogens at the same time; in addition Rj cannot be a halogen or alkoxy. The position taken by the office that adjacent homologs and positional isomers are obvious variants is improper.

Yamamoto does not present any evidence to one skilled in the art to modify naphthyl compounds. With regards to position of substituents, Yamamoto teaches away from the claimed compounds.

Yamamoto compounds are not intended for antiviral activities. Thus anticipating structurally similar compounds to possess similar properties against the common wisdom in medicinal chemistry and thus is improper. The instantly claimed compounds have surprising properties. It is highly unlikely for one of skill in the art to predict these findings.

Response:

The claimed compounds are acyl guanidines wherein the acyl portion are groups with substituents commonly used in the medicinal chemistry art arrive at alternate forms of known pharmacophore:

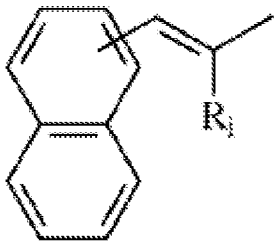


wherein the Yamamoto et al. (and others see 2nd paragraph on page of the previous office action) have substituted with routinely used organic groups and substituents to arrive at large number of acyl guanidines with pharmacological properties.

With regards to difference in biological activity, i.e., antiviral activity, note that: “[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art’s functioning, does not

render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342,1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. Yamamoto is silent with respect to antiviral activity.

Further, a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See In re Hirao, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 195.

Positional isomers (for example as shown for instantly claimed variable for instant R1 = 

), having the same radical on different positions of the molecule, are prima facie obvious, and require no secondary teaching. The experienced Ph.D. synthetic organic chemist, who would make Applicants' compounds, would be motivated to prepare these position isomers based on the expectation that such close analogues would have similar properties and upon the routine nature of such position isomer experimentation in the art of medicinal chemistry. It would be routine for the chemist to vary the

point of attachment in order to increase potency and to establish better patent protection for her compounds. In re JONES 74 USPQ 152 (4-methyl naphthyl-1-acetic acid and 2-methyl naphthyl-1-acetic acid obvious over a reference teaching 1-methyl naphthyl-2-acetic acid), quoted with approval by Ex parte MOWRY AND SEYMOUR 91 USPQ 219, Ex parte Ullyot 103 USPQ 185 (4-hydroxy-1-oxo-1,2,3,4-tetrahydroisoquinoline obvious over a reference teaching 4-hydroxy-2-oxo-1,2,3,4-tetrahydroquinoline), "[p]osition isomers are recognized by chemists as similar materials", Ex parte BIEL 124 USPQ 109 (N-ethyl-3-piperidyl diphenylacetate obvious over a reference teaching N-alkyl-4-piperidyl diphenylacetate), "[appellant's arguments] do not, in any way, obviate the plain fact that appellant's DACTIL is an isomer of McElvain et al.'s compound. This close relationship places a burden on appellant to show some unobvious or unexpected beneficial properties in his compound in order to establish patentability", Ex parte Henkel 130 USPQ 474, (1-phenyl-3-methyl-4-hydroxypyrazole obvious over reference teaching 3-phenyl-5-methyl-4-hydroxypyrazole), "appellants have made no comparative showing here establishing the distinguishing characteristics they allege which we might consider as evidence that the claimed compounds are unobvious. It is clear from In re Henze, supra, and the authorities it cites, that at least this much is necessary to establish patentability in adjacent homologs and position isomers (emphasis added)". In re Surrey 138 USPQ 67, (2,6-dimethylphenyl-N-(3-dimethylaminopropyl) carbamate obvious over a reference teaching 2,4-dimethylphenyl N-(3-dimethylaminopropyl) carbamate), In re MEHTA 146 USPQ

284, (2-(1-methyl)-pyrrolidylmethyl benzilate obvious over a reference teaching 3-(1-methyl)-pyrrolidylmethyl benzilate), "[t]he fact that a position isomer (emphasis added) of a compound is known is some evidence of the obviousness of that compound. Position isomerism (emphasis added) is a fact of close structural (emphasis in original) similarity …".Deutsche Gold-Und Silber-Scheideanstalt Vormals Roessler v. Commissioner of Patents, 148 USPQ 412, (1-azaphenothiazines obvious over references teaching 2-azaphenothiazines, 3-azaphenothiazines, and 4-azaphenothiazines), In re Crounse, 150 USPQ 554 (dye with para (CONH2) and ortho (OCH3) obvious over a dye with the same nucleus and meta (CONH2) and para (OCH3) group), Ex parte Allais, 152 USPQ 66, (3-□-aminopropyl-6-methoxyindole obvious over a reference teaching 3-□-aminopropyl-5-methoxyindole), In re Wiechert 152 USPQ 247, (1-methyl dihydrotestosterones obvious over a reference teaching 2-methyl dihydrotestosterones), Monsanto Company v. Rohm and Haas Company, 164 USPQ 556, at 559, (3',4'-dichloropropionanilide obvious over references teaching 2',4'-dichloropropionanilide and 2',5'-dichloropropionanilide), Ex parte Naito and Nakagawa, 168 USPQ 437, (3-phenyl-5-alkyl-isothiazole-4-carboxylic acid obvious over a reference teaching 5-phenyl-3-alkyl-isothiazole-4-carboxylic acid), "[t]his merely involves position isomers (emphasis added) and under the decisions cited, the examiner's holding of prima facie obviousness is warranted." In re Fouche, 169 USPQ 429, (10-aliphatic substituted derivatives of dibenzo[a,d]cycloheptadiene obvious over reference teaching 5-aliphatic substituted derivatives of dibenzo[a,d]cycloheptadiene). Ex parte Engelhardt,

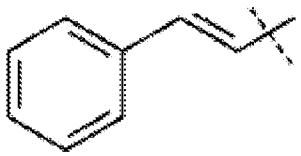
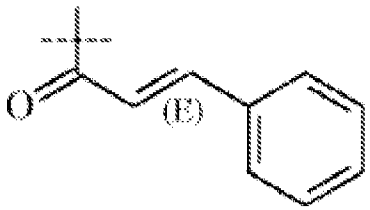
208 USPQ 343 at 349, "[i]f functional groups capable of withdrawing or repelling electrons are located in the chain or ring (emphasis added) of a biologically active compound, transfer of such groups to other positions in which their electronic effects are lessened or enhanced may alter the biological activity of the modified compound. Hence, position isomerism (emphasis added) has been used as a tool to obtain new and useful drugs", In re Grabiak 226 USPQ 870, "[w]hen chemical compounds have "very close" structural similarities and similar utilities, without more a prima facie case may be made", In re Deuel 34 USPQ2d 1210, "a known compound may suggest its analogs or isomers, either geometric isomers (cis v. trans) or position isomers (emphasis added) (e.g. ortho v. para)".

Rejection over Yamamoto and Bream:

Rejection over Bream, Arzneimittel-Forschung (1975), 25(10), 1477-82:

Applicant's argue that the Bream does not teach or suggest the claimed invention. Further Beam does not teach any motivation to combine the teachings of the prior art with those of Yamamoto to react the claimed subject matter. Beam teach phenyl compound and Yamamoto teach naphthyl compounds which are on the different side of the core pharmacophore. Further the phenyl compounds are anti-hypertensive and Yamamoto compounds are N/H inhibitory activity. As such one of skill in the art would not be motivated to extrapolate the elements of the prior art compounds to reach the claimed compounds with completely different utility.

Response:

Instantly claimed compounds are obvious variants of the prior art compound: Thus the option  of claim 1 and 1 (and cinnamoylguanidine, of claim 161) relates to desfluoro analogs of Beam compound and positional isomer of the compound of instant claim 169, page 2,  on the quinidine pharmacophore). Adding or deleting substituents such as halogen are within the routine practice of medicinal chemists. What the prior art as a whole (not limiting to the teachings of Beam and Yamamoto) teaches is that acylguanidines provide medicinal chemistry opportunity to arrive at biologically active compounds, by optionally using commonly and interchangeably used substituents.

With regards to difference in biological activity, i.e., antiviral activity, note that: "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342,1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). This is because a compound and its (inherent) property are inseparable. Further, a preamble is generally not accorded any patentable weight where it merely recites

the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See In re Hirao, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 195.

Note: Applicants Remarks correspond to the previously presented prior art citations which relate to only few of the overabundance of prior art possibilities available for obviousness rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 161-163 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Cox et al. WO 00/21538.

Cox et al. teach amiloride compounds with anti-viral activity see page 15. The first compound HMA is the same as the instantly compound, listed 4th in claim 161, also corresponds to compounds of claims 1-3, 161-163 .

Cox et al. do not teach all the possible permutations and combinations of variables of formula of claim 1 or all the compounds of claim 163 and dependent claims. However, since the prior art compound falls within the scope of the instantly claimed formula, it would be obvious to one skilled in the art to make minor modifications to the structures of Cox et al. to arrive at compounds within the scope of the Applicant's claims, further because structurally similar compounds are anticipated to possess similar properties.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 161 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim is drawn to amiloride derivatives with substituents on the nitrogen. Amiloride has multiple nitrogens in its structure with replaceable hydrogens on the nitrogens. It is unclear which nitrogens carry the recited substituents. As such the intended structures are unclear.

Further Amiloride Chemical Abstracts Name 2016-88-8 is 3,5-diamino-6-chloro-*N*-(diaminomethylene)pyrazine-2-carboxamide, This art recognized name renders the structure of the claimed compounds unclear because, for example, what is the structure of the 6th recited compound.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

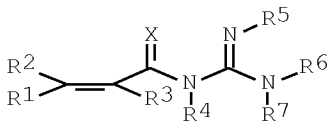
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

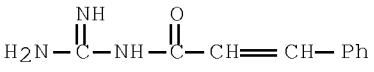
Claims 1-3, 161-163, and 169 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naik et al. IN 177137.

Naik et al. teach large number (see end of this rejection) of cinnamoylguanidines of general structure  I that reduced the duration of reperfusion-induced arrhythmias and restored cardiac contractility.

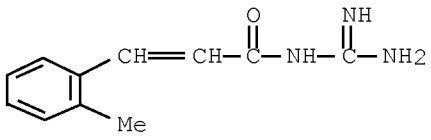
Naik et al. teach various possibilities for the R groups in the above shown generic formula, suggesting, medicinal chemistry exercise using commonly used groups as substituents on acylguanidines pharmacophore for the optimization of desired properties. Compounds of Naik et al. fall under the scope of the instantly claimed compounds of claims 1 (and dependent claims 2-3) and 169; and Naik et al also anticipates the compounds of claim 161 (and dependent claims 162-163). See end of this rejection. Naik et al are silent with respect to antiviral activity of the cinnamoylguanididines. However, a compound and its properties are inseparable. Further, a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to

stand alone. See In re Hirao, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 195.

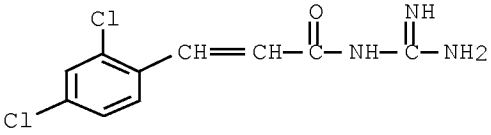
Since the prior art compound falls within the scope of the instantly claimed formula, it would be obvious to one skilled in the art to make minor modifications to the structures of Naik et al. to arrive at compounds within the scope of the Applicant's claims, further because structurally similar compounds are anticipated to possess similar properties.



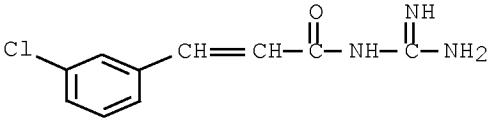
● HCl



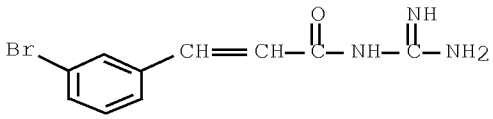
● HCl

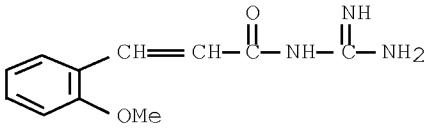


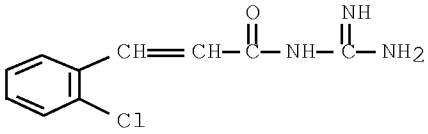
● HCl

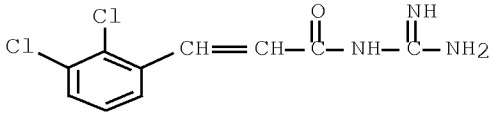


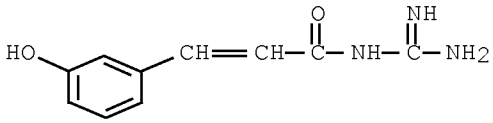
● HCl



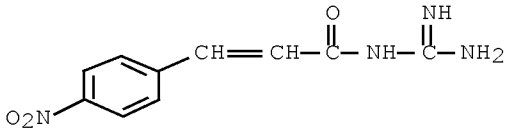


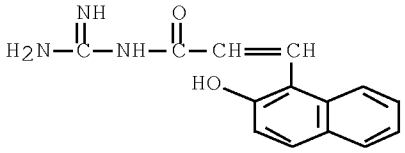


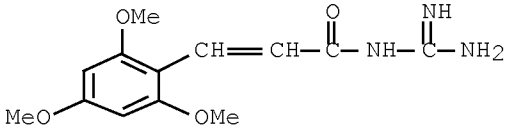




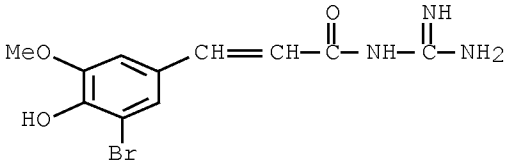
● HCl



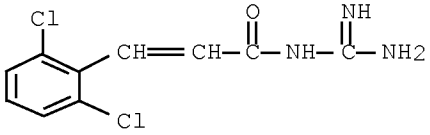




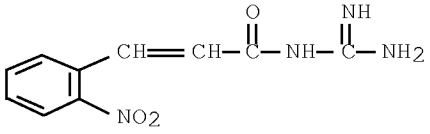
● HCl

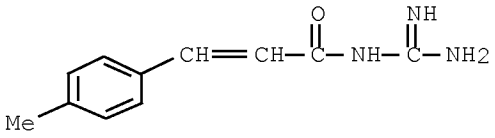


● HCl

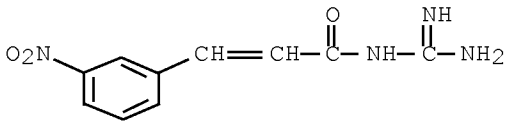


● HCl

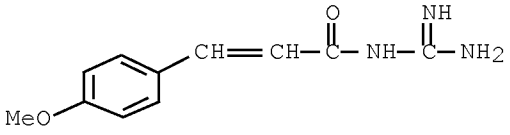




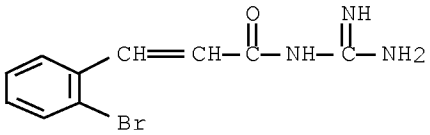
● HCl



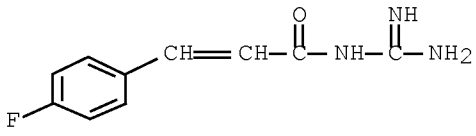
● HCl



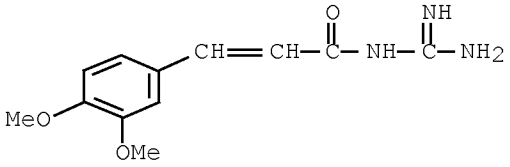
● HCl



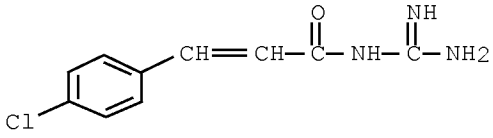
● HCl



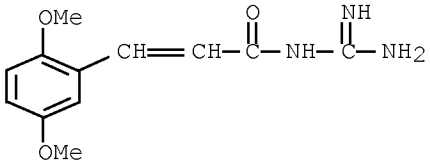
● HCl



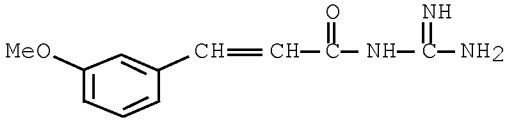
● HCl



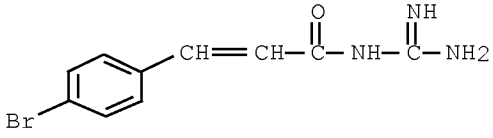
● HCl



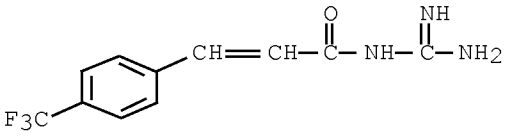
● HCl



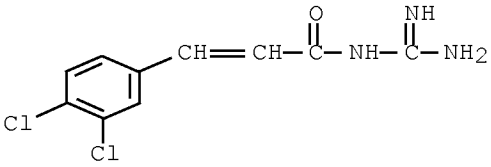
● HCl



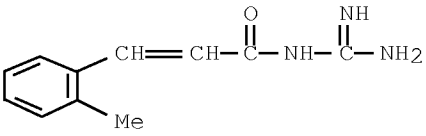
● HCl



● HCl

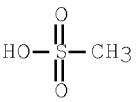


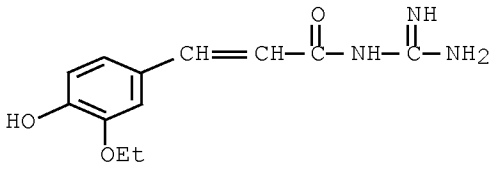
● HCl



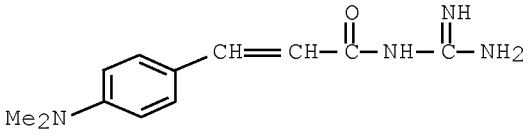
CM 2

CRN 75-75-2
CMF C H4 O3 S

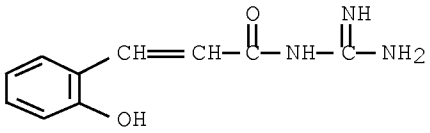




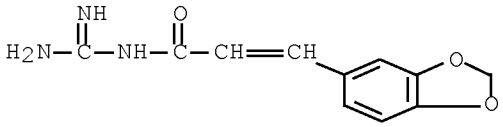
● HCl



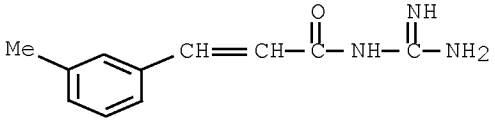
● HCl



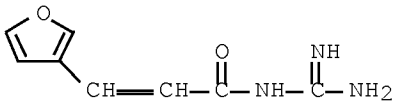
● HCl



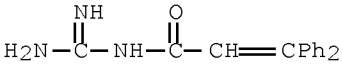
● HCl



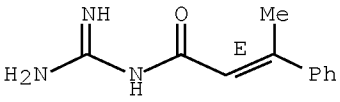
● HCl



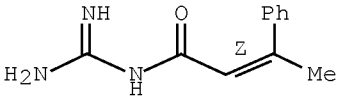
● HCl



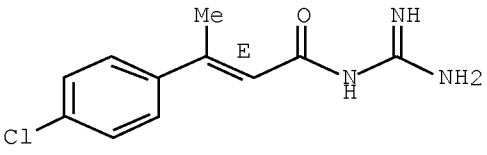
● HCl



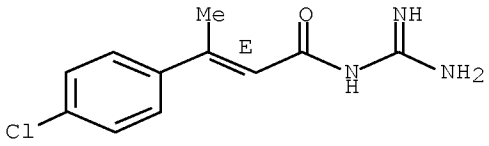
● HCl



● HCl

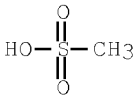


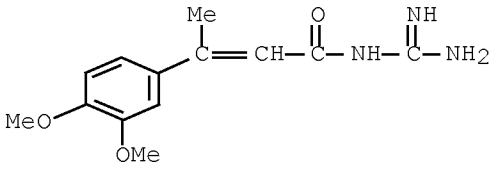
● HCl



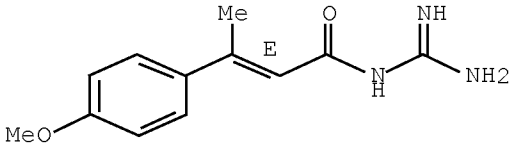
CM 2

CRN 75-75-2
CMF C H4 O3 S

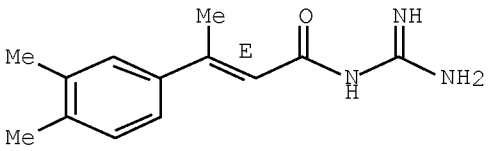




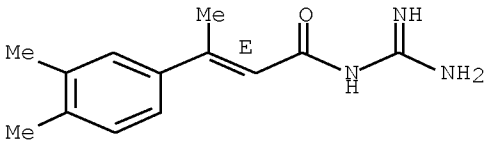
● HCl



● HCl

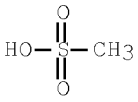


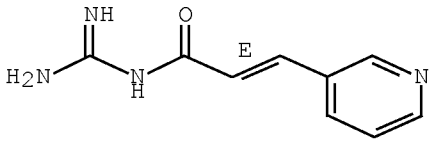
● HCl



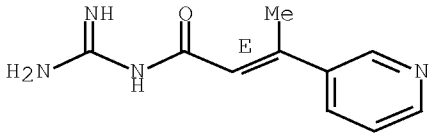
CM 2

CRN 75-75-2
CMF C H4 O3 S



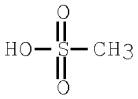


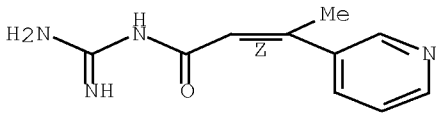
●2 HCl



CM 2

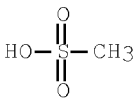
CRN 75-75-2
CMF C H4 O3 S





CM 2

CRN 75-75-2
CMF C H4 O3 S



Acyl guanidine is a well-known pharmacophore. Large number of prior art references are available for obviousness rejection: See for example. US 7041702, US 6011059, US 5733934, US 5719169, US 5567734, US 4496573.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NIZAL S. CHANDRAKUMAR whose telephone number is (571)272-6202. The examiner can normally be reached on 8.30 AM - 4.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571 0272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nizal S Chandrakumar/

Primary Examiner, Art Unit 1625